UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
ADDRESS: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,436	07/16/2001	Hermann Wagner	C1041/7010	1340

7590 03/24/2003

Alan W Steele
Wolf Greenfield & Sacks
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210-2211

EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	16

DATE MAILED: 03/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/786,436	WAGNER ET AL.
	Examiner	Art Unit
	Brian Whiteman	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-200* is/are pending in the application.

4a) Of the above claim(s) *34-103,117-200* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *104-116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6,7.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 34-171 are pending examination.

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Submitted claims 1-138 have been re-numbered as claims 34-171.

In the response to this office action, applicants must correct the claim dependency in accordance with the renumbered claims.

The examination of the elected claims is based on the claims having proper dependency in view of the renumbering of the claims.

Restrictions

Applicants' election of Group IV (claims 104-116) in Paper No. 14 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 34-103 and 117-171 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14.

Information Disclosure Statement

The U.S. Patents cited on the IDS in paper no. 6 were considered and initialed on the 1449 by the examiner. However, if the application was allowed the U.S. patents would not be printed on the patent. If the applicants want the US Patents to be printed should the application be allowed, the applicants should submit a 1449 listing the class/subclass for each US Patent listed on the 1449.

Drawings

The draftsman for the reasons on the PTO 498 objects to the drawings. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because of the following informalities: On page 30, last line, the G-motif ODN GR1 is not labeled as SEQ ID NO: 17.

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

In addition, the disclosure is objected to because of the following informalities: a heading for each section is missing.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino

acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 104-116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a tumor in a vertebrate subject comprising administering to a vertebrate subject having a tumor an oligonucleotide comprising the sequence N1-N2-G-N3-G, wherein N2 and N3 are G, wherein the oligonucleotide does not comprise a CG dinucleotide, in order to treat the vertebrate subject, does not reasonably provide enablement for a method of treating a tumor in a subject comprising administering to a subject having a tumor an oligonucleotide comprising the sequence N1-N2-G-N3-G, wherein N2 and N3 are not G. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to administering an oligonucleotide to a subject with a tumor to treat said tumor. The field of the invention lies in oligonucleotide therapy for treating a tumor in a subject.

The state of the art at the time the application was filed and currently as exemplified by Lipford et al. (Immunology, 101:46-52, 2000) teaches that poly-guanosine motifs co-stimulate antigen-reactive CD8 T cells. Lipford teaches that G quartet structures may be involved in T-cell stimulation, because at least four, but not less than four consecutive G bases are conditional for stimulation (page 51).

The specification provides examples that illustrate the properties of G-motif ODN (pages 24-37). In example 1, several G motifs failed to induce TNF in an *in vitro* culture of J774 cells. Example 8 displays that G-motif (ODN PZ2) induced NK activity *in vivo* in experimental mice. Example 10 displays that single stranded ODN, but not double-stranded ODN co-stimulate T cells in vitro.

In view of the In Re Wands Factors, the as-filed specification enables one skilled in the art to use the claimed method for treating a tumor in a vertebrate subject comprising administering an oligonucleotide comprising the sequence N1-N2-G-N3-G, wherein N2 and N3 are G, wherein the oligonucleotide does not comprise a CG dinucleotide. However, the art of record teaches that a poly G with fewer than a G quartet is not capable of stimulating an immune response in a mammal (see Lipford). The specification does not provide sufficient guidance or factual evidence for one skilled to use an oligonucleotide comprising the sequence selected from the consisting of GAGGG or GGGAG, GTGGG, or GGGTG to treat a tumor in a subject. Thus, the specification is not enabled to practice the claimed embodiment.

Furthermore, with respect to the term "subject" in the claimed methods, the specification does not define the breadth of the term "subject". The scope of the term reads on any subject (vertebrate or non-vertebrate.). The specification and the art of record is absent for treating a

tumor in a non-vertebrate subject using oligonucleotide therapy (e.g., poly G nucleic acid). The art of record teaches that vertebrate subjects respond to poly G nucleic acids, but the art of record and the specification are absent about non-vertebrate subjects responding to a poly G nucleic acid. It is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of vertebrate subject to the full scope of the claimed invention embracing any subject (non-vertebrate) that would generate a treatment of any type of tumor using the claimed method.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made provide enablement for a method of treating a tumor in a vertebrate subject comprising administering to a vertebrate subject having a tumor an oligonucleotide comprising the sequence N1-N2-G-N3-G, wherein N1 represents any nucleotide if N2 and N3 are G, but not for the full scope of the claimed methods. Given that oligonucleotide therapy wherein any oligonucleotide was employed to treat a tumor in any subject was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to oligonucleotide therapy method for treating any type of tumor in any subject or using a poly G with fewer than four contiguous Gs, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of nucleic acid therapy.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 104, 105, 106, 109, 110, 111, 112, 113, 114, and 115 are rejected under 35 U.S.C. 102(e) as being anticipated by Zupi (US Pat. 6,080,727, EFD 3/26/96). Zupi teaches a method of inhibiting a tumor comprising administering an oligonucleotide (ODN) to a patient, wherein said oligonucleotide is at least 13 bases in length (e.g. SEQ ID NOs: 6, 10, or 17) and has a phosphorothioate linkage (column 36, lines 20-67) and does not comprise a CG dinucleotide. In addition, the method comprises administering an oligonucleotide where the ODN represents the 3' terminus of the ODN (SEQ ID NO: 17) or is RNA (column 5, lines 33-46). The nucleotide sequences (SEQ ID NO: 6, 10, and 17) used in the method taught by Zupi meet the sequence requirement in claim 104 (column 36, claim 32).

Claims 104, 105, 107, 108, 109, 110, and 114 are rejected under 35 U.S.C. 102(b) as being anticipated by Iversen et al. (US Pat. 5,6543,890). Iversen teaches a method of inhibiting

cancer cells comprising contacting a cell with oligonucleotide said oligonucleotide having a nucleotide sequence consisting of a single human telomeric repeat motif (see column 25, line 19-column 26, line 58), wherein the nucleotide sequence does not contain a CG dinucleotide and has a phosphorothioate backbone modification. The oligonucleotide can include one or more modifications of the nucleic acid (column 3, lines 19-37). The oligonucleotide represents 3' terminus of the oligonucleotide. The sequences taught by Iversen meet the sequence requirement of the claimed method (see column 25, claims 7, 9, or 11).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 104 and 116 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Iversen et al. (US Pat. 5,643,890) or Zupi (US Pat. 6,080,727, EFD 3/26/96) taken with Kuby (Immunology, 2nd edition, W.H. Freeman Company, 1994). Iversen or Zupi teach a method of treating a tumor in a subject comprising administering an oligonucleotide to the subject, wherein the oligonucleotide does not have a CG dinucleotide. However, neither Iversen nor Zupi teach using a tumor-specific antigen in combination with said method.

However, at the time the invention was made, tumor-specific antigens were well known in the art for treating a patient with a tumor as evident by Kuby (pages 588-592).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of either Iversen or Zupi with Kuby to use a tumor-specific antigen with an oligonucleotide to treat a tumor in a subject. One of ordinary skill in the art would have been motivated to enhance the claimed method by combining the method with a tumor-specific antigen.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Conclusion

WO 98/32462 is cited on the 892 because it was accidentally crossed out on the 1449.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

D. PRIEBE, PH.D
EXAMINER